

Superimposed over the drug formulation/enhancer reservoir 21 of device 20 is an impermeable backing 25 and an adhesive overlay 26. Backing layer 25 is preferably impermeable to the drug and permeation enhancer and is preferably slightly larger than zone 24 in order to prevent the materials in zone 24 from adversely interacting with the adhesive in overlay 26. Other fastening means may be utilized such as an in-line contact adhesive as described above. In addition, a removable liner (not shown) would preferably be provided on the device prior to use and removed prior to application of the device 20 to the skin 27.

[00055] The rate controlling membranes may be fabricated from permeable, semi-permeable, or microporous materials which are known in the art to control the rate of drugs into and out of delivery devices or are disclosed in the aforementioned patents previously incorporated herein by reference. Suitable materials include, but are not limited to, polyolefins including polyethylene, polyvinyl acetate and ethylene vinyl acetate copolymers. High density polyethylene and ethylene vinyl acetate copolymers represent preferred rate controlling membrane materials according to the present invention.

[00056] Various materials suited for the fabrication of the various layers of the transdermal devices of FIGS. 1-3 are known in the art or are disclosed in the aforementioned patents previously incorporated herein by reference. For example, the matrix making up the drug reservoir / permeation enhancer reservoir of Figures 1-3 can be a gel or polymer and may comprise an aqueous or non-aqueous composition. For example, suitable matrix materials include, without limitation, natural and synthetic rubbers or other polymeric material, thickened mineral oil, silicone fluids, polysiloxanes, polyacrylates, ethylene vinyl acetate copolymers, or petroleum jelly.

[00057] In addition to any drug and permeation enhancer, the matrix, if needed, may also contain stabilizers, dyes, pigments, inert fillers, tackifiers, excipients and other conventional components of transdermal delivery

devices as are known in the art. The transdermal therapeutic devices of the present invention are prepared in a manner known in the art, such as by those procedures, for example, described in the patents listed previously herein.

[00058] Another preferred embodiment, depicted in Fig. 4, is directed to providing membranes for use in diffusional or osmotically driven drug delivery devices such as fluid-imbibing devices described in the patents listed above and in commonly owned copending application Serial No. 08/791,699, herein incorporated by reference. These devices can be implanted into an individual to release the drug in a controlled manner for a predetermined administration period. In general, these devices work by imbibing fluid from the outside environment and releasing corresponding amounts of the drug. The volumetric delivery rate of these systems is determined by the design, dimensions, and material properties of the rate controlling membrane and is tightly correlated to the water uptake of the membrane materials. The higher the water uptake of the membrane materials, the higher the water permeation rate through the membrane.

[00059] For some membrane materials, for example high water uptake hydrophilic polyurethane, the amorphous domain of the soft segments plays an important role in controlling water uptake, hence water permeation rate, of the membrane. It is expected that after processing, material membrane functionality such as water uptake and water permeation rate may change over time as phase separation occurs. Membrane annealing according to this invention accelerates morphological changes and stabilizes membrane performance, thus providing consistent and predictable membrane functionality. With semi-crystalline materials such as polyurethane, annealing also accelerates the phase separation of hard and soft segments such that crystalline (hard) segments come together to form micro-crystalline regions distributed within the continuous amorphous (soft) non-crystalline region.

Membranes annealed according to this embodiment exhibit water uptake and water permeability which are more stable than non-annealed membranes.

[00060] After annealing, the membrane is incorporated into a fluid-imbibing device as depicted in Figure 4. Fluid-imbibing device 30 comprises an impermeable reservoir 32 divided into two chambers by a piston 34. The first chamber 36 is adapted to contain a drug and the second chamber 38 is adapted to contain a fluid-imbibing agent. Preferred fluid-imbibing agents are NaCl with appropriate tableting agents such as povidone, magnesium stearate, sodium carboxy methylcellulose, water, and sodium polyacrylate. Other suitable fluid imbibing agents are the osmagents and osmopolymers described in, for example, U.S. Patent No. 5,413,572, incorporated by reference herein. Membrane 40 is positioned in sealing relationship with an interior surface of one end of the impermeable reservoir. The membrane can be a sheet-like layer or can be formed into any desired shape by well know procedures such as injection molding, extrusion, and the like. A preferred embodiment comprises a membrane plug as depicted in FIG 4. In the embodiment depicted in Fig. 4, fluid-imbibing device 30 additionally comprises flow path 42 formed between threaded back-diffusion regulating outlet 44 and threads 46 on the interior surface of reservoir 32.

[00061] The membrane 40 controls the rate at which fluid is imbibed into the device and is typically comprised of a polymeric material including, but not limited to, plasticized cellulosic materials, enhanced polymethylmethacrylate such as hydroxyethylmethacrylate (HEMA), and thermoplastic elastomeric materials such as polyurethanes and polyamides, polyether-polyamide copolymers, polyether blocked amides copolymers such as PEBAX®, thermoplastic copolyesters, and the like. Thermoplastic elastomeric materials are preferred as such materials span a wide range of water uptake and water permeability values, are injection moldable and easily processed, swell upon hydration, and are available in durometers widely used for gaskets and seals.